Anticholinergics Linked to CV Events in COPD

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The use of two widely prescribed inhaled anticholinergics significantly increased the risk of cardiovascular death, myocardial infarction, or stroke by about 58% among patients with chronic obstructive pulmonary disease, according to the findings of a meta-analysis involving 14,783 patients.

During follow-up from 6 weeks to 5 years, cardiovascular death, MI, or stroke occurred in 135 of 7,472 patients (1.8%) receiving either inhaled tiotropium bromide or ipratropium bromide for more than 30 days, compared with 86 of 7,311 patients (1.2%) receiving control therapy (relative risk 1.58). The difference was significant.

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However, inhaled anticholinergics did not significantly increase the risk of all-cause mortality, a secondary outcome of the meta-analysis (2.0% vs. 1.6% for control; RR 1.26).

"Clinicians and patients should carefully consider these potential long-term cardiovascular risks of inhaled anticholinergics in the treatment of COPD, and decide whether these risks are an acceptable trade-off in return for their symptomatic benefits," wrote Dr. Sonal Singh of Wake Forest University, Winston-Salem, N.C., and associates (JAMA 2008;300:1439-50).

In the 17 studies included in the meta-analysis, patients had a diagnosis of COPD of any severity. They had received either inhaled tiotropium or ipratropium or control, which could be placebo or active control, including inhaled β-agonists or inhaled steroid β-agonist combinations.

Inhaled tiotropium is comarketed in the United States by Boehringer Ingelheim GmbH and Pfizer Inc. under the trade name Spiriva. Ipratropium is available generically and also is marketed by Boehringer Ingelheim as Atrovent.

In a statement, Pfizer and Boehringer Ingelheim said they "strongly disagree with the conclusion reached by Singh et al.," and added that, "patients and physicians can be confident that Spiriva is a safe and effective medication." The two companies released a new analysis of 30 controlled trials involving 19,545 patients with COPD. That analysis showed no increased risk of all-cause mortality, cardiac mortality, stroke, or MI (http://us.boehringer-ingelheim.com/newsroom/2008/09-23-08_spiriva_safety.html).

The analysis includes unpublished data from the industry-sponsored UPLIFT (Understanding Potential Long-Term Impacts on Function With Tiotropium) trial, which were scheduled to be presented at a European Respiratory Society meeting in Berlin.

Earlier, Boehringer Ingelheim informed the Food and Drug Administration that ongoing safety monitoring had identified a "possible increased risk of stroke" in a safety analysis of 29 trials involving about 13,500 patients. That analysis estimated the risk of stroke was 8 patients/1,000 patients treated for 1 year with Spiriva, and 6 patients/1,000 per year for those treated with placebo (www.fda.gov/cder/drug/early_comm/tiotropium.htm).

The investigators of the current meta-analysis acknowledged that the analysis was limited by the quality of reported data. Many of the trials analyzed were small and short term, resulting in few events.

"As a result of small numbers, the 95% [confidence intervals] are wide, resulting in some uncertainty as to the precise magnitude of the observed risk," Dr. Singh and associates wrote. "None of these trials was specifically designed to monitor the risk of cardiovascular events, which were not adjudicated."

A sensitivity analysis restricted to the five long-term studies (ranging from 48 weeks to 5 years) involving 7,267 patients confirmed the significantly increased risk of cardiovascular death, MI, and stroke (2.9% vs. 1.8% for controls; RR 1.73). However, there was no statistically significant increase in these events in a sensitivity analysis of the 12 short-term trials (ranging from 6 weeks to 26 weeks) involving 7,516 patients (0.6% vs. 0.6%; RR 1.16).

Dr. Singh and coauthor Dr. Yoon K. Loke of the University of East Anglia (England), Norwich, called for prospective, adequately powered trials with adjudication of cardiovascular events to assess the safety of inhaled anticholinergics in patients with COPD. The authors reported no financial disclosures. ■

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